Upadacitinib in psoriatic arthritis with prior TNF-inhibitor failure: a 56-week real-world study

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Abstract

Objective

Evidence on the long-term real-world effectiveness and safety of upadacitinib in TNFi-refractory psoriatic arthritis (PsA) remains limited. Our aim was to evaluate the real-world effectiveness and safety of upadacitinib in PsA patients with prior TNF-inhibitor failure.

Methods

This retrospective study included 47 patients with PsA (mean age 46.7 ± 10.1 years, 59.6% female, mean disease duration 9.8 ± 7.4 years). Patients received upadacitinib 15 mg daily and were followed up to 56 weeks. Clinical activity (DAPSA, BASDAI, ASDAS-CRP), ACR responses, PASI, patient-reported outcomes, and adverse events were assessed at baseline, week 12, 24, and 56. Intention-to-treat (ITT) analysis was the primary approach.

Results

Axial involvement was present in 74.5% and enthesitis in 85.1%. At week 12, ITT ACR20/50/70 response rates were 63.8%, 55.3%, and 31.9%, respectively. By week 56, ITT responses were 61.7%, 59.6%, and 51.1%. Significant improvements were also observed in DAPSA, BASDAI, ASDAS-CRP, and PASI scores (all $p<0.001$), with resolution of enthesitis in most patients. Adverse events occurred in 23.4% of patients, with 10.6% leading to discontinuation. Safety outcomes were consistent with the established profile of upadacitinib, with no new safety signals identified.

Conclusion

Upadacitinib demonstrated sustained efficacy across musculoskeletal and skin domains in PsA patients with prior inadequate response to TNF inhibitors, with a safety profile consistent with previous reports. These findings support its role as an effective treatment option in this difficult-to-treat population.

Key words

psoriatic arthritis, upadacitinib, Janus kinase inhibitor, TNF-inhibitor failure, real-world evidence, safety, treatment outcomes

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Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory disease that affects up to 30% of individuals with psoriasis and is characterised by its clinical heterogeneity, encompassing peripheral arthritis, axial involvement, enthesitis, dactylitis, and nail disease (1-3). Beyond its musculoskeletal manifestations, PsA has profound systemic consequences, including impaired physical functioning, reduced health-related quality of life, and an increased prevalence of metabolic and cardiovascular comorbidities (4, 5). This phenotypic diversity poses unique challenges in disease management and necessitates a domain-based, individualised treatment approach (6).

The advent of tumour necrosis factor inhibitors (TNFi) marked a significant milestone in PsA therapy, offering substantial improvements in disease control and patient outcomes. However, real-world treatment responses remain suboptimal, with approximately 30–40% of patients discontinuing therapy due to primary inefficacy, secondary loss of response, or tolerability issues (7, 8). Importantly, the proportion of PsA patients achieving low disease activity (LDA) or remission with TNFi therapy is consistently lower than that observed in other inflammatory rheumatic diseases such as rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) (9).

This discrepancy can be partly attributed to the multifaceted nature of PsA, which involves both synovial and extrasynovial tissues. Unlike RA or axSpA, treatment of PsA must address inflammation in multiple domains simultaneously – an inherently more complex task (10). In the TICOPA trial, which implemented a tight control strategy in early PsA, only 62% of patients receiving TNFi achieved minimal disease activity (MDA) by week 48, a figure notably lower than the 70–80% LDA/remission rates commonly reported in RA trials (11). Similarly, a multicentre Italian cohort (GISEA) reported 12-month DAS28-LDA rates exceeding 60% in RA, while only 42% of PsA patients reached the same threshold (12). In axSpA, pooled observational data indicate that approximately 65–75% of patients treated with TNFi achieve ASDAS-LDA or better within the first year (13).

Another complicating factor is the relatively modest efficacy of biologic agents in controlling enthesitis and dactylitis, two hallmark features of PsA that often persist despite suppression of articular inflammation. While TNFi demonstrate superiority over placebo in these domains, response rates for enthesitis and dactylitis remain variable and often fall short of clinical expectations (14, 15). Moreover, the assessment of these non-synovial features is less standardised and subject to interobserver variability, which complicates both clinical evaluation and treatment targeting (16).

Against this background, targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), particularly Janus kinase (JAK) inhibitors, have emerged as promising therapeutic alternatives. These agents modulate intracellular signalling cascades implicated in PsA pathogenesis, including those involving interleukin (IL)-23, IL-6, and interferon-γ pathways (17). Upadacitinib, a selective JAK1 inhibitor, has shown consistent efficacy in both biologic-naive and TNFi-experienced PsA populations. The SELECT-PsA 1 and SELECT-PsA 2 trials demonstrated that upadacitinib significantly improved musculoskeletal and cutaneous outcomes, with sustained efficacy and acceptable safety profiles (18). Notably, SELECT-PsA 2, which enrolled patients with prior bDMARD failure, reported superior ACR responses and substantial improvements in patient-reported outcomes compared to placebo (19).

Despite these encouraging results, real-world data on the long-term effectiveness and safety of upadacitinib in TNFi-refractory PsA patients remain limited. Moreover, there is a particular lack of evidence from middle-income countries and public hospital settings, where patient profiles may differ significantly from those in clinical trials.

Randomised controlled trials (RCTs), while essential for establishing efficacy, often do not fully reflect the complexity of clinical practice due to stringent eligibility criteria and protocolised

management (20). Real-world evidence (RWE), therefore, plays a crucial role in validating the external generalisability of RCT findings and in evaluating treatment persistence, safety, and effectiveness across heterogeneous patient populations (21).

To address this evidence gap, we conducted a 56-week real-world observational study in a tertiary care centre in Turkey, focusing on PsA patients with prior inadequate response to at least one TNFi. We aimed to assess the clinical effectiveness and safety profile of upadacitinib, including its impact on disease activity, cutaneous involvement, adverse events, and treatment continuation over time.

Methods

Study design and setting

This retrospective, single-centre, real-world observational study was conducted at the Department of Rheumatology, Denizli State Hospital, a tertiary referral centre for inflammatory rheumatic diseases in western Turkey. The study period extended from October 27, 2023, to April 30, 2025. All clinical and laboratory data were extracted from the hospital's electronic rheumatology registry system, which is routinely maintained by trained personnel. The study was conducted in full compliance with the ethical principles of the Declaration of Helsinki and all relevant national regulations. The protocol was reviewed and approved by the Local Ethics Committee (approval no: E-60116787-020-615478 of November 27, 2024). Written informed consent was obtained from all participants prior to enrolment. To safeguard privacy, all patient data were anonymised before analysis, ensuring the highest standards of confidentiality.

Patient selection

Adult patients (aged ≥18 years) who fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) were considered eligible. Inclusion criteria were as follows: i. active PsA despite previous exposure to at least one tumour necrosis factor inhibitor (TNFi), ii. initiation of upadacitinib 15 mg/day, iii. availability of at least 12 weeks of follow-up data after treatment initiation. Patients with a history of malignancy, coexisting systemic autoimmune rheumatic diseases (*e.g.* systemic lupus erythematosus, rheumatoid arthritis), or incomplete clinical documentation were excluded. The date of upadacitinib initiation was defined as the index date (baseline, week 0).

Data collection

Baseline demographic and clinical characteristics, including age, sex, body mass index (BMI), disease duration, HLA-B27 status, and comorbidities, were documented. PsA phenotype (axial *vs.* peripheral) was recorded based on clinical evaluation and MRI-confirmed sacroiliitis when available. Axial involvement was defined according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial spondyloarthritis, requiring inflammatory back pain together with MRI or radiographic evidence of sacroiliitis in the context of CASPAR-confirmed psoriatic arthritis. Data on prior and concomitant therapies (*e.g.* csDMARDs, corticosteroids) were collected. Concomitant csDMARDs (mainly methotrexate, leflunomide, or sulfasalazine) and low-dose corticosteroids (≤10 mg/day prednisolone equivalent) were allowed to continue if the dose remained stable for at least 4 weeks before upadacitinib initiation and throughout follow-up. Dose escalation or tapering was not permitted during the study period unless clinically indicated.

Clinical and laboratory assessments were performed at four predefined timepoints: baseline (week 0), week 12, week 24, and week 56. Disease activity was evaluated using the following parameters: Disease Activity in Psoriatic Arthritis (DAPSA), Visual Analogue Scale for pain (VAS-pain, 0–100 mm), tender joint count (TJC, 68 joints), swollen joint count (SJC, 66 joints), C-reactive protein (CRP, mg/L), and Health Assessment Questionnaire (HAQ). For patients with active skin disease, the Psoriasis Area and Severity Index (PASI) was recorded. Axial disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP). Adverse events (AEs) were monitored throughout follow-up and classified based on clinical severity. Safety assessments specifically included surveillance for herpes zoster, serious infections, venous thromboembolism (VTE), major adverse cardiovascular events (MACE), and malignancies. Laboratory parameters – including complete blood count, liver enzymes, renal function tests, and lipid profile – were routinely evaluated at baseline and every 12 weeks during follow-up. Adverse events were documented at each visit and graded by clinical severity.

Although formal MedDRA coding was not used, AEs were categorised based on rheumatologist clinical judgment.

Longitudinal trends were graphically illustrated for DAPSA, BASDAI, ASDAS-CRP, and ACR responses (Fig. 1). Clinical outcomes are summarised in Tables I-IV. ACR20/50/70 responses were determined according to the American College of Rheumatology core set criteria, based on improvement from baseline in tender and swollen joint counts and at least three of the following five parameters: patient and physician global assessments, pain VAS, HAQ-DI, and CRP.

Treatment persistence and discontinuation

Drug discontinuation was defined as permanent cessation of upadacitinib for any reason. Reasons for discontinuation were categorised into the following groups: primary non-response (lack of meaningful clinical improvement by week 12), secondary loss of efficacy (initial response followed by disease worsening), or adverse events/patient decision. Patients who permanently discontinued therapy before week 12 were excluded from longitudinal effectiveness analyses but were included in the safety evaluation and the intention-to-treat (ITT) responder analysis, where they were classified as non-responders.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software (v. 28.0, IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarise baseline characteristics and clin-

ical outcomes. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution, and categorical variables as absolute numbers and percentages.

Longitudinal changes in clinical parameters (*e.g.* DAPSA, TJC, SJC, CRP, VAS-pain, HAQ) were assessed at baseline, week 12, week 24, and week 56 using pairwise comparisons. The Wilcoxon signed-rank test was applied for non-parametric variables, and the paired t-test for normally distributed variables such as BASDAI and HAQ. To adjust for multiple comparisons, Bonferroni correction was applied.

Responder rates for ACR20, ACR50, and ACR70 were calculated using both an on-treatment approach (including only patients still receiving upadacitinib at the respective timepoints) and a conservative intention-to-treat (ITT) approach, in which all patients who discontinued treatment were considered non-responders.

PASI analyses were conducted only between baseline and week 56 due to unavailability of intermediate timepoint data. Axial outcomes were assessed using BASDAI and ASDAS-CRP.

Drug discontinuation was analysed descriptively, with reasons categorised as primary non-response, secondary loss of efficacy, adverse events, or patient decision. No imputation was performed for missing data; all analyses were based on observed cases only. Subgroup analyses were not conducted due to limited sample size. Statistical significance was defined as an adjusted p-value <0.05.

Results

Baseline characteristics

A total of 47 patients with TNFi-refractory psoriatic arthritis (PsA) were included. The mean age was 46.7±10.1 years, and 59.6% were female. Table I summarises the baseline demographic and clinical characteristics of the study population.

Treatment response and disease activity over time - ACR responses

At week 12, ACR20/50/70 response rates were 63.8%, 55.3%, and 31.9% of

Table I. Demographic and baseline clinical features.

Parameters	Patients, n=47
Age, years	46.7 ± 10.1
Female gender, n (%)	28 (59.6)
Disease duration, mean±SD	9.8 ± 7.4
Education status,	
Elementary School	17 (36.2)
Secondary School	16 (34.0)
High School	8 (17.0)
Bachelor's degree	5 (10.6)
Master's degree	1 (2.1)
Smoker, ever	24 (51.1)
Alcohol, ever	6 (12.8)
BMI	28.1 ± 3.9
Arthritis	21 (44.7)
Enthesitis	40 (85.1)
Dactylitis	12 (25.5)
Inflammatory back pain	36 (76.6)
History of psoriasis	37 (78.7)
Current presence of psoriasis on scalp or skin	19 (40.4)
Family history of pso	28 (59.6)
Nail changes	10 (21.3)
RF negativity	43 (91.5)
New bone formation on x-ray	18 (38.3)
Sacroiliac radiograph grade	
1	11 (23.4)
2	26 (55.3)
3	8 (17.0)
4	2 (4.3)
Sacroiliac MRI, sacroiliitis	35 (74.5)
HLA-B27 positivity	25 (53.2)
TJC	4 (0-14)
SJC	1.5 ± 2.1
LEI	4 (0-6)
BASDAI	6.3 ± 1.0
ASDAS-CRP	3.4 ± 0.6
DAPSA	27 (12-80)
VAS Pain (scale 0-10)	8 (6-9)
VAS Fatigue (scale 0-10)	8 (5-10)
PtGA (scale 0–10)	7 (6-10)
PGA (scale 0–10)	5 (3-9)
HAQ	0.8 ± 0.4
ESR	16 (0-68)
CRP	7.1 (2-53)
PASI	0 (0-63)
Comorbidities	
HT	14 (29.8)
DM	11 (23.4)
Obesity	16 (34.0)
Hyperlipidaemia	18 (38.3)
Chronic lung disease	5 (10.6)
CVD	5 (10.6)
Cancer	0 (0)
Depression	23 (48.9)
IBD	2 (4.3)
Treatment	
NSAID	47 (100.0)
HCQ	5 (10.6)
LEF	12 (25.5)
SSZ	34 (72.3)
MTX	24 (51.1)
Steroid	26 (55.3)
History of previous use of biological drugs	47 (100.0)
When?	2 (4.3)
6 months ago	2 (4.3)
Within the last 6 months	45 (95.7)
Adalimumab	24 (51.1)
Golimumab	9 (19.1)
Certolizumab pegol	10 (21.3)
Infliximab	4 (8.5)
Etanercept	17 (36.2)
Tofacitinib	5 (10.6)
Secukinumab	14 (29.8)
Ixekizumab	3 (6.4)
Ustekinumab	2 (4.3)

Table II. ACR response rates at week 56.

ACR response	ITT analysis (n=47)	On-treatment analysis (n=29)
ACR20	61.7%	100%
ACR50	59.6%	96.6%
ACR70	51.1%	82.8%

The table presents the comparative ACR20/50/70 response rates at week 56 for the entire cohort (intention-to-treat, ITT) and for the subgroup of patients who continued upadacitinib therapy through week 56 (on-treatment analysis).

patients (n=47), respectively. By week 56, 29 patients (61.7%) remained on upadacitinib and were included in the on-treatment efficacy analysis. Among them, ACR20, ACR50, and ACR70 responses were achieved by 100%, 96.6%, and 82.8% of patients, respectively. The high ACR response rates observed at week 56 primarily reflect outcomes among patients who remained on treatment, indicating potential responder-retention (on-treatment) bias. Therefore, intention-to-treat analyses were also performed, conservatively considering patients who discontinued therapy as non-responders. When patients who discontinued treatment were conservatively considered as non-responders (intention-to-treat analysis), week 56 ACR20/50/70 response rates were 61.7%, 59.6%, and 51.1%, respectively (Table II).

- Joint and axial involvement

Tender joint count (TJC) significantly decreased from a median of 4 at baseline to 0 by week 24 (p=0.002), and swollen joint count (SJC) also showed early and sustained improvement (p=0.019). At baseline, 70.2% of patients had active enthesitis (LEI >0). The proportion achieving complete resolution (LEI = 0) increased steadily from 29.8% at week 12 to 55.9% at week 24, reaching 72.4% among on-treatment patients and 44.7% in the ITT analysis at week 56. The reduction in LEI scores was statistically significant compared with baseline (p=0.024 at week 24; p<0.001 at week 56), indicating a progressive and sustained improvement in enthesitis severity over time (Table III).

Axial disease indices demonstrated robust reductions: BASDAI decreased from 6.3±1.0 to 2.5±0.8 by week 56, and ASDAS-CRP declined from 3.4±0.6 to 2.0±1.6. These changes were statistically significant at week 12 and remained stable thereafter (Table III). Longitudinal trends in DAPSA, BASDAI, and ASDAS-CRP are visualised in Figure 1.

- Composite scores and global assessments

Absolute improvements from baseline were observed across all major clinical domains. By week 56, the mean DAPSA score decreased by 15.4 points (95% CI: 10.9–19.9), BASDAI by 3.8 (95% CI: 2.9–4.7), and ASDAS-CRP by 1.4 (95% CI: 1.0–1.8), indicating a clinically meaningful reduction in disease activity. DAPSA scores showed substantial improvement, decreasing from a baseline median of 27 (IQR: 12–80) to 14 (4–42) at week 12 (p<0.001), and further to 9 (4–31) by week 56. Both VAS-pain and VAS-fatigue scores declined significantly over time (p<0.001), in

Table III. Clinical parameters, clinimetric test, and clinical response to the upadacitinib therapy.

	Baseline	w12, n=47	p^a	w24, n=35	p^b	w56, n=29	p^c
no. of patients (%)	47 (100.0)	47 (100.0)	–	35 (74.5)	–	29 (61.7)	–
Disease Clinimetric Indexes							
TJC	4 (0-14)	1.5 (0-14)	**0.002**	0 (0-10)	1.000	0 (0-6)	1.000
SJC	1.5 ± 2.1	0.32 ± 0.55	**0.019**	0.11 ± 0.40	1.000	0.07 ± 0.37	1.000
ACR20	–	30 (63.8)	–	33 (94.3)	0.365	29 (100.0)	1.000
ACR50	–	26 (55.3)	–	27 (77.1)	0.226	28 (96.6)	1.000
ACR70	–	15 (31.9)	–	17 (48.6)	**0.002**	24 (82.8)	0.622
LEI	4 (0-6)	2 (0-5)	**0.003**	0 (0-4)	0.024	0 (0-2)	<0.001
BASDAI	6.3 ± 1.0	3.9 ± 1.2	**<0.001**	3.1 ± 1.5	0.070	2.5 ± 0.8	1.000
ASDAS-CRP	3.4±0.6	2.1±0.6	**<0.001**	2.0 ± 0.6	0.237	2 ± 1.6	1.000
DAPSA	27 (12-80)	14 (4-42)	**<0.001**	11 (4-35)	0.196	9 (4-31)	1.000
VAS pain (0-10)	8 (6-9)	4 (1-7)	**<0.001**	3 (1-7)	0.622	2 (1-6)	0.622
VAS fatigue (0-10)	8 (5-10)	4.5 (1-8)	**<0.001**	3 (1-8)	1.000	2 (1-6)	1.000
PtGA (scale 0–10)	7 (6-10)	4 (1-9)	**<0.001**	3 (1-7)	0.151	2 (1-6)	1.000
PGA (scale 0–10)	5 (3-9)	3 (1-8)	**<0.001**	2 (1-5)	0.622	2 (1-4)	1.000
HAQ	0.8 ± 0.4	0.5 ± 0.3	**<0.001**	0.5 ± 0.3	0.115	0.4 ± 0.3	1.000
ESR	16 (0-68)	12 (2-49)	**0.002**	16 (2-75)	0.359	19 (2-77)	1.000
CRP	7.1 (2-53)	2.2 (0-19)	**0.002**	3 (0-25)	1.000	4 (1-25)	1.000
PASI*	0 (0-63)	–	–	–	–	0 (0-3)	**<0.001**

ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score/C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, DAPSA Disease Activity in Psoriatic Arthritis, HAQ Health Assessment Questionnaire; LEI: Leeds Enthesitis Index; PASI: Psoriasis Area Severity Index; PGA: Physician Global Assessment; PtGA: Patient Global Assessment; SJC: swollen joint count; TJC: tender joint count; VAS: fatigue Visual Analogue Scale for fatigue; VAS pain: Visual Analogue Scale for pain. Statistical analysis conducted using Stata software (Paired Student's t test).
p-value significant (in bold) if <0.05; p^a between baseline and w12, p^b between w12 *vs*. w24 and p^c between w24 *vs*. w52, * p^c between baseline and w52.
LEI: Leeds Enthesitis Index; enthesitis resolution was defined as LEI = 0. Statistically significant improvement observed at week 24 (p=0.024) and week 56 (p<0.001, Wilcoxon signed-rank test). Absolute changes (Δ) and 95% confidence intervals (CIs) for key outcomes (DAPSA, BASDAI, ASDAS-CRP) are reported in the *Results* section.

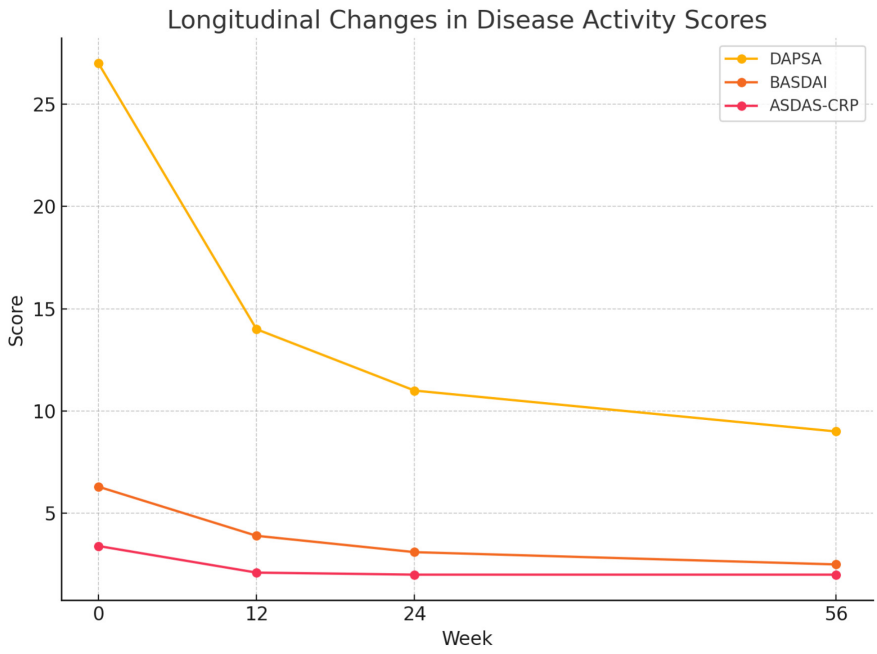

Fig. 1. Longitudinal changes in disease activity scores (DAPSA, BASDAI, ASDAS-CRP) over 56 weeks, demonstrating a marked and sustained reduction from baseline.

Table IV. Adverse events during upadacitinib therapy (n=47).

Adverse event	number of patients (n)	Percentage (%)
None	36	76.6%
Creatine kinase elevation	2	4.3%
Acne	2	4.3%
Cytopenia	1	2.1%
Cough	1	2.1%
Esophagitis	1	2.1%
Hair loss	1	2.1%
Liver enzyme elevation	3	6.4%

The table summarises the distribution of adverse events observed among patients receiving upadacitinib for TNFi-refractory psoriatic arthritis over a 56-week follow-up period.

parallel with improvements in PtGA and PGA scores. HAQ scores also improved from 0.8±0.4 to 0.4±0.3 (p<0.001). All clinimetric changes and p-values are detailed in Table III.

- Cutaneous response

Among the 19 patients with active skin psoriasis at baseline, the PASI score decreased from a median of 0 (0–63) to 0 (0–3) by week 56 (p<0.001).

- Safety and drug retention

Adverse events occurred in 11 patients (23.4%), with 5 cases (10.6%) leading to discontinuation (Table IV). The most common adverse events included transaminase elevation, acne, and mild gastrointestinal symptoms. There were no serious infections, cardiovascular events, or deaths reported. Overall, 18 patients (38.3%) discontinued treatment during follow-up due to the following reasons: primary non-response (n=5), secondary loss of efficacy (n=4), adverse events (n=5), patient decision (n=3), and pregnancy planning (n=1).

Discussion

This 56-week real-world study, conducted in a Turkish patient population, offers important insights into the clinical performance and tolerability of upadacitinib in psoriatic arthritis (PsA) patients with an inadequate response to tumour necrosis factor inhibitors (TNFi) (17-21). Biologic and targeted synthetic therapies have expanded treatment options, particularly for patients with suboptimal responses to conventional agents (6, 7, 12). However, individuals with prior biologic failure are often underrepresented in randomised controlled trials (RCTs) and typically present with longer disease duration and a more refractory disease course (18, 19). Our findings contribute to the expanding body of real-world evidence on JAK1 inhibition. Upadacitinib appears to be a feasible therapeutic option even in more heterogeneous and treatment-refractory PsA populations (19-21). Upadacitinib demonstrated rapid and durable improvements across multiple domains, including peripheral joints, axial symptoms, and entheseal involvement (18, 24). Notably, reductions in DAPSA, BASDAI, and ASDAS-CRP scores were observed throughout the 56-week period, underscoring the broad musculoskeletal efficacy of the drug (18, 20). These outcomes are mechanistically consistent with the pharmacodynamic effects of selective JAK1 inhibition, which modulates key proinflammatory pathways – including IL-6, IL-12/23, TNF-α, and IFN-γ – known to be central in both axial and peripheral PsA pathophysiology (22, 23).

Entheseal inflammation, a notoriously difficult-to-treat domain in PsA, also showed marked improvement over time, as assessed by the Leeds Enthesitis Index (24, 25). This supports the drug's efficacy in addressing deep-tissue inflammation, further strengthening its musculoskeletal profile. In our cohort, the prevalence of enthesitis (85%) and axial involvement (74.5%) was notably higher than that reported in broader PsA populations (approximately 35% and 25–70%, respectively) (6, 17, 25). This discrepancy likely reflects the selected nature of our study population, consisting exclusively of TNF-inhibitor-refractory patients. Previous studies have shown that biologic-resistant phenotypes are more likely to exhibit axial and entheseal predominance, representing a distinct clinical subset with higher inflammatory burden and poorer treatment response (14, 15, 17, 25). Moreover, the use of the Leeds Enthesitis Index (LEI), which assesses a limited number of entheseal sites compared to more comprehensive indices such as SPARCC (16), may have contributed to

the apparent overrepresentation of active enthesitis in this sample.

Among patients who remained on therapy through week 56, ACR20/50/70 response rates reached 100%, 96.6%, and 82.8%, respectively – substantially exceeding the corresponding rates reported in the SELECT-PsA 2 trial (26). Nevertheless, these differences must be interpreted with caution. Unlike the strict intention-to-treat (ITT) framework used in RCTs, our study reports both on-treatment and conservative ITT analyses, the latter treating all discontinuations as non-responders. Under this approach, ACR20/50/70 rates at week 56 declined to 61.7%, 59.6%, and 51.1%, respectively – aligning more closely with phase 3 results and reflecting the complexities of real-world clinical settings (18, 19).

Real-world cohorts are inherently more heterogeneous, often encompassing patients with multiple comorbidities, varied treatment histories, and fluctuating adherence (9, 12, 20). Thus, the integration of observational data is critical for contextualising RCT findings and ensuring external validity. While our results support the clinical utility of JAK1 inhibition in refractory PsA, large-scale prospective trials remain necessary to define its role within the therapeutic landscape (19, 20). Comparisons of treatment outcomes across rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), and psoriatic arthritis (PsA) should be interpreted cautiously, as these diseases differ in immunopathogenic mechanisms, clinical domains, and outcome measures (8, 17, 28). Reported response and remission rates across indications are not directly comparable; therefore, such cross-disease contrasts in this study are presented solely to provide clinical context rather than to imply efficacy equivalence.

Patient-reported outcomes (PROs) improved meaningfully as early as week 12, including significant reductions in VAS-pain, VAS-fatigue, and HAQ scores. These domains are highly relevant in clinical practice, as they directly influence treatment satisfaction, daily functioning, and long-term adherence (27, 28). Our results align with findings from other real-world studies involving JAK inhibitors in PsA and broader spondyloarthritis populations (19, 20, 27). For example, data from the US-based CorEvitas registry showed that tofacitinib-treated PsA patients experienced significant improvements in pain, fatigue, and HAQ-DI over a six-month period (27). Similarly, a multinational observational study reported that JAK inhibitors led to clinically meaningful enhancements in PROs, including fatigue and quality of life, in patients with axial spondyloarthritis (28). These findings highlight the dual impact of JAK1 inhibition on both objective disease activity and subjective disease burden (17, 23).

With regard to cutaneous response, statistically significant improvement was observed in our cohort. However, interpretation must consider context: most patients had previously received IL-17 and/or TNF inhibitors and exhibited low baseline PASI scores – possibly reflecting musculoskeletal-dominant phenotypes commonly seen in rheumatology clinics (14, 19). This may have resulted in a ceiling effect, potentially underestimating the dermatologic efficacy of upadacitinib in biologic-naive populations (24, 25).

In terms of safety, the overall incidence of adverse events (23.4%) and discontinuations due to side effects (10.6%) was consistent with previous phase 3 and post-marketing data (18, 19, 26). For instance, the 56-week SELECT-PsA 2 trial reported a serious adverse event rate of 2.6 per 100 patient-years, with no emergent safety signals (26). Longer-term pharmacovigilance studies also support the stability of the safety profile of upadacitinib (18, 19). In our cohort, most adverse events were mild to moderate in severity, and no serious infections, cardiovascular events, or malignancies were reported (26, 29). Integrated safety analyses from SELECT-PsA trials similarly revealed no new significant safety concerns, and rates of MACE, malignancy, and serious infections remained comparable to those in control groups (18, 26, 29).

Despite this favourable safety profile, treatment discontinuation – whether due to primary or secondary inefficacy, or adverse effects – may result in slightly lower drug persistence compared to TNF inhibitors (7, 20, 29). In our cohort, 61.7% of patients (29 out of 47) remained on upadacitinib at week 56. This is consistent with registry data; for example, a German real-world PsA cohort reported 5-year drug survival rates of 62.3% for TNF inhibitors and 53.3% for JAK inhibitors, with a significant difference favouring TNFi (29). These findings suggest that long-term adherence may be somewhat lower for JAK inhibitors, particularly when used as second- or third-line options following biologic failure (19, 20).

A key strength of this study is its contribution to the limited real-world literature on JAK1 inhibitors in Turkey, based on data obtained from tertiary public hospitals (9, 19, 20). This enhances the generalisability of our findings across socioeconomically diverse patient populations and complements data generated in academic settings. Given the scarcity of published data on upadacitinib use following TNFi failure, our study provides timely and clinically relevant insights that address an important unmet need (19-21).

Nonetheless, several limitations must be acknowledged. The retrospective design introduces inherent risks of selection and reporting bias (12). Furthermore, the absence of imaging-based outcomes (*e.g.* radiographic progression or MRI inflammation scores) limits the assessment of structural efficacy (16, 25). Future prospective studies with comparator arms and advanced imaging endpoints are warranted to validate and expand upon these findings (17, 19, 24).

Conclusion

This 56-week real-world study provides complementary evidence supporting the effectiveness and safety of upadacitinib in patients with psoriatic arthritis who had an inadequate response to prior TNF-inhibitor therapy. Clinically meaningful improvements were observed across musculoskeletal domains – including peripheral arthritis, axial involvement, and enthesitis – as well as in patient-reported outcomes. Although the high response rates observed in on-treatment analyses are encouraging, they should be interpreted with caution

due to the lack of a comparator arm. Despite a moderate rate of treatment discontinuation, no new safety signals emerged. These findings suggest that JAK1 inhibitors such as upadacitinib may offer a viable therapeutic option in refractory PsA. However, confirmation through large-scale, prospective, head-to-head trials is essential to establish their optimal place in the treatment algorithm.

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